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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,302	01/03/2007	Makoto Yoshimoto	P29879	5398

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
07/16/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/577,302	YOSHIMOTO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-24-08&4-24-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 4-21-08 is acknowledged. The traversal is on the ground(s) that the groups share a special technical feature. This is not found persuasive because the substance and the transgenic are not linked by the same special technical feature because the substance does not have to be found using the transgenic of claim 1. The process by which the substance is found does not alter the structure of the substance. The substance does not share the special technical feature of the transgenic. Accordingly, the transgenic and the substance are not linked by a special technical feature. The requirement is still deemed proper and is therefore made FINAL. Claims 13 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4-21-08.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a nucleic acid sequence encoding mutant human α-synuclein operably linked to a tyrosine hydroxylase promoter, wherein the mutant human α-synuclein substitutes a Thr residue

for a Ala residue at amino acid residue 53 and deletes C terminal amino acid residues, and wherein the number of neurons in the substantia nigra expressing dopamine is decreased as compared to wild-type mice, does not reasonably provide enablement for making any transgenic non-human mammal having decreased dopamine-producing neurons in the substantia nigra, making a transgenic mouse having decreased dopamine-producing neurons in the substantia nigra using a nucleic acid sequence encoding any α-synuclein or any promoter, or using any "portion thereof" of a transgenic non-human mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a transgenic non-human mammal or a portion thereof, wherein an α-synuclein gene is introduced and the gene is expressed in the neurons, and the number of dopamine-producing neurons in the substantia nigra is significantly decreased as compared with that of a wild- type animal. The claims encompass making any non-human mammal using a nucleic acid encoding any α-synuclein operably linked to any promoter.

However, the art at the time of filing taught a transgenic mouse comprising a nucleic acid sequence encoding mutant A30P and A53T human α-synuclein operably linked a tyrosine hydroxylase (TH) promoter (Matsuoka (Neurobiology of Disease, June 2001, Vol. 8, pg 535-539), pg 536, "Generation of transgenic mice"). The number of dopamine-producing neurons in the substantia nigra was the same as wild-type mice (pg 537, Table 1; last two sentences of abstract). Similarly, Rathke-Hartlieb (J.

Neurochem., 2001, Vol. 77, pg 1181-1184) taught transgenic mice comprising a nucleic acid sequence encoding mutant A30P human α-synuclein operably linked to the TH promoter did not have decreased dopamine-producing neurons in the substantia nigra as determined by TH staining (pg 1182, "transgenic mice"; first two paragraphs of "Results and Discussion" on pg 1183). Masliah (Science, Feb. 2000, Vol. 287, pg 1265-1268) taught a transgenic mouse comprising a nucleic acid sequence encoding wild-type human α-synuclein operably linked to a platelet-derived growth factor-β (PDGF-β) promoter (pg 1266, lines 1-4; Fig. 1A) that had the same density of TH-positive neurons in the substantia nigra as non-transgenic controls (pg 1268, col. 1, last 5 lines); however, TH-positive nerve terminals within the striatum were decreased in transgenic mice as compared to non-transgenic littermates (Fig. 3B; pg 1268, sentence bridging col. 1-2).

The specification teaches making a transgene construct comprising a mutant A53T human α-synuclein operably linked to a tyrosine hydroxylase promoter (pg 16, Example 2). It is assumed pg 17, last 6 lines taken with pg 2, last 5 lines, means the mutant A53T human α-synuclein has a deletion in the C terminus. The specification teaches making transgenic mice with the construct (pg 19, Example 4). Transgenic mouse line 1702 expressed the mutant human α-synuclein in dopamine neurons (pg 26, first line of last full paragraph) and had decreased numbers neurons in the substantia nigra expressing tyrosine hydroxylase (TH) (pg 35, last 4 lines; Fig. 11A and 11B). Dopamine producing cells in the substantia nigra were known in the art to be identified by TH staining (Rathke-Hartlieb, cited above; pg 1183, col. 1, "Results and Discussion",

line 26, "Most, if not all DA neurons in the substantia nigra (identified by TH staining on adjacent sections)"). Thus, transgenic mouse line 1702 taught by applicants had decreased dopamine-producing neurons in the substantia nigra as compared to wild-type mice.

The nucleic acid sequence used to make the transgenic mouse is essential to determine the phenotype of the mouse. The specification does not teach that deleting the C terminus of mutant A53T human α-synuclein is adequate to overcome the unpredictability discussed by Matsuoka, who taught the number of dopamine-producing neurons in the substantia nigra of a transgenic mouse comprising a nucleic acid sequence encoding mutant A53T human α-synuclein operably linked a tyrosine hydroxylase promoter and wild-type mouse were the same. The spec does not teach how to make transgenics having decreased dopamine-producing neurons in the substantia nigra other than with the construct in Examples 1 and 2 comprising a mutant A53T human α-synuclein with a C terminal deletion. Without such guidance it would have required those of skill in the art undue experimentation to determine the parameters required to obtain decreased dopamine-producing neurons in the substantia nigra of a transgenic as claimed using any nucleic acid sequence other than the one described by applicants. Therefore, the claim should be limited to using a nucleic acid sequence encoding mutant A53T human α-synuclein with a C terminal deletion operably linked to a tyrosine hydroxylase promoter.

In addition, the specification does not enable those of skill to make a transgenic non-human mammal having decreased TH-positive neurons in the substantia nigra

other than mice. Claim 1 encompasses making any transgenic non-human mammal. The specification suggests making rodents, such as mice, hamsters, guinea pigs, rats and rabbits as well as chickens, dogs, cat, goats, cattle, pigs, monkeys. First, chickens are not mammals. Second, the state of the art at the time of filing was that the phenotype of transgenic non-human mammals was unpredictable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (pg 277, col. 2, lines 17-27). Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit unpredictable phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) described spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same

transgenes that successfully caused the desired symptoms in transgenic rats. Thus, those of skill could not predict whether a phenotype in transgenic mice would be obtained in other species of non-human mammals. The specification fails to make any correlative guidance that the phenotype obtained in the 1702 line of mice would be obtained in other non-human mammalian species. Without such guidance, it would have required those of skill undue experimentation to determine the parameters required to obtain non-human mammals having decreased dopamine-producing neurons in the substantia nigra as claimed other than mice.

Claim 1 encompasses a "portion thereof" of a transgenic non-human mammal. The specification contemplates using a portion of the transgenic on pg 11, including the head, fingers, paws, legs, abdominal region, tail, cells and organs of the non-human mammal. The specification does not teach how to use any "portion" listed on pg 11. Without such guidance, merely listing examples of "portions" of the transgenic without teaching how to use them is not an enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear when the number of dopamine-producing cells in the substantia nigra is "significantly" decreased as compared to wild-

type. Applicants have not drawn the line where a decrease is significant; therefore, those of skill would not know when they were infringing on the claim.

Claim 3 is indefinite because "in a manner" does not clearly set forth the structure of the variant human α-synuclein. The claim should clearly set forth the human α-synuclein has a substation of a Thr residue for an Ala residue at amino acid residue 53.

Claim 5 is indefinite because it is unclear how it further limits claim 1. As written, the claim does not further limit the α-synuclein gene as being part of a recombinant DNA or that the α-synuclein gene is operably linked to a promoter capable of expression in dopamine-producing neurons.

Claim 6 is indefinite because "the promoter" lacks antecedent basis in claim 1.

Claim 7 is indefinite because it is unclear to what it refers. It does not state the transgenic has decreased intracerebral dopamine levels as compared to a wild-type control.

Claim 7 is indefinite because the metes and bounds of what applicants consider "early" are not defined in the specification or the art at the time of filing.

Claim 8 is indefinite because it is unclear to what it refers. It does not state the transgenic has at least an 85% decrease in intracerebral dopamine levels as compared to a wild-type control.

Claim 9 is indefinite because it is unclear to what it refers. It does not state the transgenic has at least an 80% decrease in intracerebral TH levels as compared to a wild-type control.

Claim 10 is indefinite because it is unclear to what it refers. It does not state the transgenic has at least a 60% decrease in spontaneous locomotor activity as compared to a wild-type control.

Claims 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: administering a compound to the transgenic of claim 1 and a control, and comparing a feature of the transgenic to the control and determining whether the substance has "dopamine-like action." The structure of the control, what is compared and how it is determined whether the substance has "dopamine-like action" are all unclear.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner